II. REMARKS

Upon further consideration by the Examiner of the arguments in the Appeal Brief filed August 8, 2005, the Examiner withdrew the finality of the previous Office Action in favor of the rejection of the present Office Action. In the present Office Action, the Examiner withdrew the rejection of claims 1, 4, 6, 8-20 and 24-32 under 35 U.S.C. 102(b) as being anticipated by Barry et al. (U.S. Patent No. 5,055,306). Applicants acknowledge with appreciation the Examiner's withdrawal of this rejection.

A. Status of Claims

Claims 1, 4, 6, 8-20, 24-33 and 35-39 are pending in this application. The claims are not being amended in this response.

B. 35 U.S.C. §103 Rejection over U.S. Patent No. 5,055,306 to Barry et al.

In the Office Action, claims 1, 4, 6, 8-20, 24-33 and 35-39 were rejected under 35 U.S.C. §103(a) "as being unpatentable over Barry et al (US 5,055,306).

In making the rejection, the Examiner stated the following:

> [T]he disclosure of a sustained release formulation where the antidiabetic agents metformin and tolbutamide can be active agents meets the limitation of the broad claim to sustained release formulation where the active agent is metformin, therefore, the broad claim to sustained release metformin formulation reads on the disclosure of Barry. With respect to the function or property of the metformin formulation, it is noted as stated in MPEP 2112.02 [R-2] II, 'Products of identical chemical composition can not have mutually exclusive properties." A chemical chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.
>
> Therefore, administration of product/composition that is essentially the same as the claimed formulation would exhibit the properties/functions recited in the pending claims. Absent a showing of factual evidence, the metformin formulation of Barry would have the properties and functions recited in the instant claims.

Office Action at page 3. (*citation omitted*)

This rejection is traversed. U.S. Patent No. 5,055,306 to Barry et al. (hereinafter "Barry") relates to a granular sustained-release formulation of a pharmacologically active substance presented in the form of a tablet. (See, e.g., Abstract, and col. 3, lines 36-39) The tablet purportedly includes a sufficient amount of granules to provide a predetermined dose or a number of doses of the pharmacologically active substance and effervescent or water-dispersible ingredients. (See, e.g., Abstract and col. 3, lines 39-42). Each of the granules allegedly includes a core including one or more pharmacologically active substances and preferably one or more excipients and a coating covering substantially the whole surface of the core including a water insoluble (but water swellable) acrylic polymer and a water soluble hydroxylated cellulose derivative. (See, e.g., Abstract and col. 3, lines 42-53).

It is respectfully submitted that Barry fails to teach or suggest a sustained release formulation comprising an active agent consisting of metformin or a pharmaceutically acceptable salt thereof which provides "an AUC which is increased by the presence of food as compared with administration in the fasting state" as recited in independent claims 1, 6, 8, 9, 12, 15, 18, 24, and 27. Further, it is respectfully submitted that Barry fails to teach or suggest a sustained release formulation comprising an active agent consisting of metformin or a pharmaceutically acceptable salt thereof "which does not exhibit a decrease in the bioavailability of metformin if taken with food" as recited in independent claim 31; and fails to teach or suggest the methods of claims 33 and 35.

Contrary to the Examiner's assertion, Barry does not teach the same or substantially the same dosage forms of the present invention, and therefore, the functional limitations of the presently claimed invention would <u>not</u> be necessarily present in the dosage forms Barry. Barry exemplifies, for example, making granules of the active ingredient and microcrystalline cellulose, coating the granules with a solution of eudragit and hydroxypropylmethylcellulose,

preparing granules of an effervescent base, and forming tablets containing a mixture of the granules containing the active ingredient and those of the effervescent base.

Thus, in the examples of Barry, the tablet is formed of coated granules. Further, Barry states in column 4, lines 6-9 that the formulations are tablets which disintegrate into sustained release granules upon coming into contact with an aqueous liquid.

In contrast, the exemplified formulations of the present application are formed by making granules of the active ingredient (metformin) and a binder, tableting the granules, optionally seal coating the core tablet, and then spray coating the seal coated tablet (not the granules) with a sustained release coating cellulose acetate, a flux enhancing agent (PEG 400), and a plasticizer.

In the present examples, a core tablet is formed, then the entire tablet is coated with sustained release coating-granules, as opposed to Barry which describes the granules as being sustained release coated.

Therefore, it cannot be said that the formulations of Barry are the same or substantially the same as the formulations of the present application. As such, it cannot be stated that the functional limitations of the presently claimed invention would be necessarily present in the dosage forms of Barry.

Further, it is respectfully submitted that a sustained release metformin formulation which provides "an AUC which is increased by the presence of food as compared with administration in the fasting state." as recited in claims 1, 6, 8, 9, 12, 15, 18, 24, and 27, or a sustained release dosage form including metfomin or a pharmaceutically acceptable salt thereof which "does not exhibit a decrease in the bioavailability of metformin if taken with food" as recited in claim 31, would not have been expected by one of ordinary skill in the art when viewing the prior art as a

whole, including the Physician's Desk Reference, (50th edition, pages 752-757) Glucophage®, previously cited by the Examiner and submitted herewith as Exhibit 1.

For example, on page 753, middle column, Physician's Desk Reference states that "food ***decreases*** the extent of and slightly ***delays*** the absorption of metformin, as shown by approximately a 40% lower mean peak concentration (Cmax), ***a 25% lower area under the plasma concentration versus time curve (AUC)*** and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting." (*emphasis added*). Therefore, it is respectfully submitted that the prior art as a whole teaches away from an increase in the bioavailability (as measured by AUC) of metformin in the presence of food. It is respectfully submitted that one of ordinary skill in the art would have no expectation of a dosage form which provides an increase in AUC and bioavailability as recited in the present claims, and instead would expect a similar effect as recited in the Physician's Desk Reference such as e.g., a decreased AUC and bioavailability in the presence of food. Furthermore, there is no teaching or suggestion in Barry that would lead one to expect anything different than what was already known.

With respect to independent claims 33 and 35, Applicants further note the following:

Independent claim 33 recites a method of treating a human diabetic patient with an oral solid dosage form of metformin, comprising **swallowing** on a once a day basis in the presence of food an **intact** controlled release dosage form . . . ." (emphasis added). Similarly, independent claim 35 recites a method of treating diabetes in humans, comprising **swallowing** on a once a day basis in the presence of food an **intact** controlled release dosage form . . . ." (emphasis added).

It is respectfully submitted that Barry is directed to effervescent or water dispersible dosage forms which are administered by disintegrating the dosage form in an aqueous liquid prior to administration (See, e.g., col. 5, lines 43-55 of Barry) or by sucking and swallowing material released from the tablet (See, e.g., col. 10, lines 46-54 of Barry). Barry fails to teach or suggest a **method of treatment** comprising "...**swallowing** an **intact** dosage form..." as recited in independent claims 33 and 35, nor would one of ordinary skill in the art be motivated to do so in view of Barry as the dosage forms of Barry are not meant to be swallowed intact.

In addition, it is respectfully submitted that Barry actually **teaches away** from the presently claimed invention, as the very purpose of Barry is counter-intuitive to the Appellants presently claimed invention of claims 33 and 35. The formulations of the Barry reference are described as "presented in the form of tablets which disintegrate into sustained-release granules upon coming into contact with an aqueous liquid." (See *Barry et al.* at Col. 4, lines 6-9). This purportedly overcomes the difficulties associated with conventional sustained-release formulations, enabling large dosages in sustained-release form to be more easily administered to, and swallowed by, the patient. (See *id.* at Col. 2, lines 61-68).

In view of Barry, one of ordinary skill in the art would not be motivated to treat a human patient comprising swallowing an intact controlled release dosage form as recited in claims 33 and 35 of the present invention, as the tablets of the Barry reference are formulated to disperse or effervesce in the mouth of the patient upon administration.

In view of the above remarks with respect to Barry, the Examiner is requested to remove this rejection.

C. Conclusion

It is respectfully submitted that in view of the actions taken an arguments presented, that this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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